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Comment on "Carbamylated Erythropoietin Ameliorates Cyclosporine Nephropathy Without Stimulating Erythropoiesis"

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Dear editor:

We read with great interest the recently published article by Abe et al., in the esteemed journal *Cell Transplantation*, entitled "Carbamylated Erythropoietin Ameliorates Cyclosporine Nephropathy Without Stimulating Erythropoiesis" (1). In an experimental study on 6-week-old male rats, which were treated with cyclosporine (CsA), they found that carbamylated erythropoietin (CEPO) suppressed macrophage infiltration and phenotypic alteration of interstitial myofibroblasts and interstitial fibrosis in the CsA nephropathy model. They also observed that CEPO administration decreased the transforming growth factor (TGF)-β1 mRNA levels in cyclosporine-treated kidneys. In this study, tubular apoptosis was persistently stimulated after CsA treatment, while CEPO significantly inhibited tubular apoptosis. They concluded that CEPO administration reduced CsA-induced tubulointerstitial injury in two ways: by protection of tubular epithelial cells from apoptosis and inhibition of interstitial fibrosis (1). We congratulate Abe et al. for their work; however, we would like to point out our findings on the kidney-protective effect of erythropoietin (EPO). In a study to evaluate the ameliorative effects of EPO on tubular cells, we studied 40 male Wistar rats (Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran) with a weight range of 200–250 g. They were randomly allocated to four groups of 10 each. Of them, there was a special group, in which the rats first received gentamicin (100 mg/kg) for 10 days, then 100 U/kg EPO [Eprex (Epoetin Alfa), Janssen Cilag, Ltd., Switzerland] was injected intraperitoneally for the next 10 days, and the rats were sacrificed at the 20th day, and the kidneys were removed for histopathologic study (2). All specimens were examined for six morphologic parameters including epithelial cell vacuolization, degeneration, tubular cell flattening, hyaline cast, tubular dilatation, and debris materials in tubular lumen on semiquantitative scores from 1 to 5, while the score of 0 was assigned to the normal tissue without damage (4,5). EPO was able to prevent the increase in serum creatinine and blood urea nitrogen. Furthermore, coadministration of gentamicin and EPO reduced effectively the kidney tissue damage compared to the control group. Our study showed the renal protective effect of erythropoietin, when the drug is given in combination with gentamicin. However, the protective property of EPO was also evident when the drug was applied after gentamicin-induced tubular damage, and it was revealed that the drug was still effective after installation of tissue injury (2). This indicates that EPO may have curative effects, besides its preventive properties (2). Hence, the study of Abe et al. supported the beneficial effects of EPO in renal transplant patients and also supported renoprotective properties of EPO beyond anemia correction (2,3,5,7). Thus, EPO is a promising kidney-protective agent to prevent, ameliorate, or attenuate tubular damage induced by gentamicin or other nephrotoxic agents such as CsA (1,6). Interestingly, they showed that CEPO treatment was not accompanied by enhancing or reducing the hemoglobin concentration. Hence, to reduce CsA nephrotoxicity using EPO, especially CEPO, is a reasonable suggestion by Abe et al. (1). In this regard, to better understand the preventive properties of erythropoietin, more experimental or clinical studies are suggested.

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